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Pilot Study on Sentinel Node Biopsy in Breast Cancer

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Background and Objectives: Sentinel node biopsy (SNB) in breast cancer using indigo carmine was started in January 1998, and this method has proved feasible and reliable. From our initial experience, sentinel lymph nodes (SLNs) were identified in 65 of 88 cases of breast cancer (74%).
Methods: Lymphatic mapping in breast cancer was assessed using radionuclide, technetium-99m human serum albumin or technetium-99m tin colloid. A pilot study on SNB with dye or a combined method was performed between August 1998 and January 1999.
Results: SLNs were identified in 55 of 59 cases (93%). False-negative SLNs were found in 2 cases. The sensitivity and accuracy in all cases were 92% and 96%. SLNs in 52 cases were also diagnosed by immediate frozen sectioning. The sensitivity and accuracy were 89% and 96%.
Conclusions: SNB in the combined method was the best way to identify SLNs in breast cancer.
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KEY WORDS: **breast cancer; sentinel node biopsy; sentinel lymph nodes; lymphatic mapping; indigo carmine**

INTRODUCTION

The first lymph nodes to drain a primary tumor are referred to as sentinel lymph nodes (SLNs). According to the SLN hypothesis, histologically negative SLNs can guarantee the histological negativity of the remaining regional lymph nodes (non-SLNs). Feasibility studies on sentinel node biopsy (SNB) have been reported in melanoma, breast cancer, thyroid cancer, and so on [1–4]. SNB in breast cancer has been examined since the early 1990s [2]. Avoiding axillary lymph node dissection (ALND) should decrease arm morbidity in breast cancer patients. SNB may be a reasonable alternative to unnecessary ALND and a suitable method for local control of early breast cancer. We began a feasibility study on SNB with indigo carmine (Daiichi Pharmaceutical, Tokyo, Japan) in January 1998, and this method proved feasible and reliable [5]. To improve the SNB surgical procedure, we investigated lymphatic mapping of SLNs with dye and radionuclides. Our pilot study on SNB in breast cancer and the clinical issues in Japan are reported.

MATERIALS AND METHODS

Fifty-eight female patients with stage 0–IIIB breast cancer, including 1 patient with bilateral breast cancer, underwent surgical treatment between August 1998 and January 1999. A total of 59 cases were evaluated in this series. Informed consent about lymphatic mapping and SNB was obtained before the surgical procedure.

Under general anesthesia, 5 ml of indigo carmine (20 mg) was injected subcutaneously at 2 or 3 sites around the primary tumor or near the scar after excisional biopsy, and the breast lesions were rubbed well for about 30 sec. A small incision was performed in the axilla 15 min after dye injection. Once the subcutaneous fat pad

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was dissected bluntly, the blue-stained lymph nodes or dye-filled lymphatic tracts were easily identified in a few minutes. Whenever blue-stained afferent lymphatic tracts were traced to lymph nodes which were partially stained blue, they were excised as SLNs. Total mastectomy or breast-conserving surgery (BCS) was then performed. ALND was completed up to level I, II, or more.

Lymphoscintigraphy was performed in 43 of 59 cases during this 6-month period. Since technetium-99m (^{99m}Tc) sulfur colloid and ^{99m}Tc-colloidal albumin are not available in Japan, 1 of the 2 permitted kinds of ^{99m}Tc-labeled agent, ^{99m}Tc human serum albumin (^{99m}Tc-HSA) or ^{99m}Tc tin colloid (^{99m}Tc-TC) (Nihon Medi-Physics, Tokyo, Japan), was used for lymphatic mapping. The day before the operation, 30–50 MBq (0.8–1.4 mCi) of ^{99m}Tc-HSA or ^{99m}Tc-TC in 2.5 ml of saline was injected subcutaneously at 2 or 3 sites around the primary tumor or near the scar after excisional biopsy. Preoperative lymphoscintigraphy of the involved breast and the axillary region in the anterior and anterior-oblique projections was performed using a large-field scintillation camera. About 24 hr after tracer injection, total mastectomy or BCS was performed following an SNB. The scintigraphic hot spots in vivo were detected using a hand-held gamma-ray detector (Navigator; USSC, Norwalk, CT), or radioactive lymph nodes ex vivo were identified using a portable scintillation survey meter. Usually, SLNs had 2- to 8-fold radioactivity compared to non-SLNs as the background, which was counted at around 0.1 microsievert (μSv)/hr by a scintillation survey meter.

Exposure of the surgeon's fingers and chest to radiation in the operating room was monitored using a dosimeter-ring and film-badge. The lower limit of detectable radiation dose is 0.1 mSv/month.

The pathological diagnosis was based on examination of paraffin-embedded hematoxylin and eosin–stained sections of the primary tumor and all axillary lymph nodes. SLNs were also diagnosed histologically by immediate frozen-section examination.

RESULTS

Clinicopathological variables and SNB are summarized in Table I. Ultimately, 55 (93%) of 59 cases succeeded in SNB with dye or the combined method. SLNs were found in level I of the axilla, where the number ranged between 1 and 6 nodes and the mean and median numbers were 2.5 and 2 nodes. The number of non-SLNs ranged between 9 and 43 (median 17). Following dye-guided SNB, the identification rate of SLNs rose from 65 (74%) of 88 cases in our initial experience [5] to 48 (81%) of 59 cases during this 6-month period. Using lymphoscintiscans after tracer injection, hot spots such as SLNs were visualized in 28 (65%) of 43 cases. Hot spots belonged to level I of the axilla in 23 cases and to levels I and II in 1 case. Three cases had hot spots in level I, and parasternal lymph nodes, which were examined in only 1 case, were found to be histologically negative. One case had a hot spot in level III alone without lower levels of the axillary lymph nodes but failed in SNB with the combined method. Finally, 34 (79%) of the 43 cases resulted in successful SNB with a gamma-ray detector, while SNB with the combined method showed an excellent identification rate (98%). In this series, 2 cases had negative SLNs with 1 node-positive case that was not a SLN. According to SNB with dye, gamma-ray detector, the combined method, and dye or the combined method, the sensitivities ranged between 88% and 92% (false-negative rates 8%–12%, Table II). In 13 (52%) of the 25 cases with node-positive breast cancer, SLNs were the only lymph nodes affected and all non-SLNs were nega-

TABLE I. Clinicopathological Variables and Identification of Sentinel Lymph Nodes (SLNs)

Variables	No. of cases	SLN identification rate (%)
Age (years)		
≤35	1	100
36–50[a]	28	89
≥51	30	97
Tumor size (cm)		
0.0–2.0	13	85
2.1–3.0	21	90
3.1–5.0	25	100
Clinical nodal status		
N0	40	90
N1	18	100
N2	1	100
Clinical stage		
0, I	12	83
IIA	28	93
IIB	18	100
IIIB	1	100
Dominant primary site		
Lateral	35	91
Medial or central	24	96
Type of surgery		
Mastectomy	43	98
Breast-conserving surgery	16	81
Prior excisional biopsy		
Yes	7	71
No	52	96
Histological grade		
I	9	78
II	24	92
III	26	100
Histological nodal status		
Negative	34	88
Positive	25	100
Methods of sentinel node biopsy		
Dye	59	81
Gamma-ray detector	43	79
Combined method	43	98
Dye or combined method	59	93

[a]Including 1 case with bilateral breast cancer.

TABLE II. Sentinel Node Biopsy (SNB) and Prediction of Axillary Lymph Nodes

SNB	Sensitivity	Specificity	Accuracy
Dye	92% (22/24)	100% (24/24)	96% (46/48)
Gamma-ray detector	88% (14/16)	100% (18/18)	94% (32/34)
Combined method	90% (19/21)	100% (21/21)	95% (40/42)
Dye or combined method	92% (23/25)	100% (32/32)	96% (53/55)

TABLE III. Sentinel Lymph Node (SLN) Positivity in 25 Cases of Node-Positive Breast Cancer

No. of positive SLNs	No. of cases with positive axillary lymph nodes				
	1	2	3	4–9	≥10
None	2	0	0	0	0
1	5	2	0	2	1
2	0	6	0	1	1
3	0	0	2	0	2
4	0	0	0	0	1

tive (Table III). Furthermore, SLNs in 52 cases were diagnosed by immediate frozen-section examination. SLNs were negative in 35 cases and positive in 17 cases, while microfoci of cancer cells in the permanent sections of SLNs were found in 2 of the 35 cases. The sensitivity and accuracy of SLNs examined were 89% and 96%.

The average operation time for breast surgery including SNB was about 2 hr. The levels of exposure of the surgeon's fingers and chest to radiation during the 6 months were undetectable.

DISCUSSION

SNB in breast cancer is a promising surgical technique to confirm nodal status and minimize arm morbidity. Many investigators have demonstrated excellent results of SNB with vital blue dye, radionuclides, or the combined method [6–10]. However, there are many different ideas concerning the site of injection of the vital blue dye or radionuclides, the dose of radioactivity used, the interval between dye injection or lymphoscintiscan and SNB, and the various surgical procedures for SNB in breast cancer. Lymphatic mapping and SNB remain standardized.

Isosulfan blue (Lymphazurin; Zenith Parenterals, Rosemont, IL) is used for dye-guided SNB in Western countries. However, this dye is not available in Japan. We were the first to use indigo carmine for SNB in breast cancer [5]. According to the initial experience of dye-guided SNB, the identification rates of SLNs ranged between 66% and 82% [11–14]. As Giuliano and coworkers [7,11] demonstrated, there is a learning curve in the surgical technique of lymphatic mapping and SNB. We also experienced this learning curve.

Radionuclides for lymphatic mapping should be in sizes of a few hundred nanometers, to permeate the lymphatic vessels and remain in the SLNs. However, ^{99m}Tc-HSA is too small (≤5 nm) to be retained in the SLNs and ^{99m}Tc-TC is too big (≥500 nm) to migrate through the lymphatic vessels compared with ^{99m}Tc-sulfur colloid and ^{99m}Tc-colloidal albumin. These factors influenced the low success rate (79%) of SNB with the gamma-ray detector in this study. Fortunately, SNB with the combined method was capable of improving the identification rate (98%) of SLNs, and it seems to be the best way.

We must pay attention to the radiation exposure of surgeons, pathologists, and other paramedical personnel. The theoretical radiation exposure from low-dose ^{99m}Tc-labeled agents is extremely low compared with the annual natural irradiation. The radiation dose recorded in this series was acceptable.

We experienced 2 cases of false-negative SLNs. In both cases, radioactive lymph nodes were visualized faintly on the lymphoscintiscan in delayed images 6 hr after tracer injection. In addition, 1 case showed 2 lymphatic channels to level I and internal mammary chain. Faint radioactive spots in SLNs and unexpected drainage by 2 or more lymphatic channels may result in misleading false-negative SLNs. False-negatives in large pilot studies on SNB ranged between 0% and 7% [6–10,15].

If SLNs are histologically negative using immediate frozen-section examination, ALND will be omitted. However, it may be difficult to diagnose the microfoci of cancer cells in frozen sections of SLNs. Some investigators have proposed examination of multiple sections of SLNs by immunohistochemical staining [7,9,15,16]. Using this technique, SLNs with micrometastases were detected in between 11% and 47% of node-positive cases. We experienced 2 cases with microfoci of cancer cells in the permanent sections of SLNs, while these cases had only 1 positive lymph node in SLNs. Interestingly, cases in which only the SLNs were affected ranged between 31% and 67% in node-positive breast cancer [2,5–7,9–11]. Axillary management of these cases will be one of the debatable issues regarding SNB in breast cancer.

In conclusion, SNB with indigo carmine and radionuclide was found to be the best way to identify SLNs in breast cancer. An acceptable false-negative rate remains unclear, but SNB in a multicenter validation study proved feasible and predicted axillary lymph node metastases [17]. Prognosis in early breast cancer patients should be evaluated in a randomized trials, comparing SNB to ALND. However, SNB in breast cancer is expected to be performed as a standard practice in the near future.

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COMMENTARY

The concepts of sentinel lymph node (SLN) biopsy for accurate staging of breast cancer continue to proliferate around the world, even in countries with traditionally low rates of breast cancer, as exemplified by the Japanese experience. It is interesting, however, that the concepts employed by our Japanese colleagues mirror closely the experiences of both single-institution and multiinstitutional reports. The study supports the idea that the combination of dye and radionuclide expands the opportunity of identification of the SLN from 74% to 93%. A false-negative rate of 3.6% (2 of 55 identified cases) is quite acceptable and remarkable for the fact that immediate frozen sectioning with routine hematoxylin and eosin staining was used in lieu of recommended serial sectioning and immunohistochemistry of the SLN. It would be ideal if frozen section analysis of the sentinel node would prove highly accurate since the return of patients to the operating room for complete axillary dissection might be avoided.

Imoto and colleagues support the notion that minimal radioactivity is involved in this technique and that exposure of the operating team and the pathologist is not problematic. The Japanese group correctly voices a concern that this technique is still in evolution and that randomized trials which include mandatory axillary lymph node dissection should continue throughout the world. My hope is that these workers have an opportunity to use the same dyes and tracers that are routinely found in Western countries so that institutional comparisons may be more easily performed.

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